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(54) Title: COMBINATION OF A MACROLIDE T-CELL IMMUNOMODULATOR AND A CALCIFEROL FOR THE TREATMENT OF SKIN DISEASES OR OF INFLAMMATORY BOWEL DISEASE

(57) Abstract: Synergistic combinations of a macrolide T-cell immunomodulator or immunosuppressant such as 33-epichloro-33-desoxyascomycin and a calciferol such as calcipotriol or tacalcitol are provided, which are useful in particular in the treatment of dermatological diseases such as atopic dermatitis, acne and psoriasis, or of inflammatory bowel disease (IBD).

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AMENDED CLAIMS

[received by the International Bureau on 16 August 2004 (16.08.04);
original claims 1-5 replaced by amended claims 1-5]

1. A pharmaceutical composition comprising pimecrolimus in combination or association with a calciferol together with at least one pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1 wherein the calciferol is calcipotriol or tacalcitol.

3. A method of treatment of a dermatological disease such as atopic dermatitis, acne or psoriasis, or of inflammatory bowel disease (IBD), in a subject suffering from or at risk for such condition, comprising co-administering a synergistically effective amount of a composition according to claim 1.

4. A process for the preparation of a composition of claim 1 comprising mixing pimecrolimus and a calciferol in combination or association with at least one pharmaceutically acceptable diluent or carrier.

5. A kit of parts comprising pimecrolimus and a calciferol in separate unit dosage forms together with instructions for use.

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COMBINATION OF A MACROLIDE T-CELL IMMUNOMODULATOR AND A CALCIFEROL FOR THE TREATMENT OF SKIN DISEASES OR OF INFLAMMATORY BOWEL DISEASE

The invention relates to pharmaceutical compositions, for use in particular in the treatment of skin diseases. It concerns a pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant and a calciferol.

It has now been found that, surprisingly, macrolide T-cell immunomodulators and immunosuppressants, when used in combination with calciferols, act synergistically, resulting in a potentiation of pharmacological activity, such that effective beneficial, especially antipsoriatic and anti-acne activity is seen upon co-administration at dosages which would be well below the effective dosages administered individually.

The invention thus concerns novel pharmaceutical compositions comprising a **macrolide T-cell immunomodulator or immunosuppressant** in association or combination with a **calciferol**, hereinafter briefly named "the compositions of the invention".

A macrolide T-cell immunomodulator or immunosuppressant is to be understood herein as being a T-cell immunomodulator or T-cell immunosuppressant which has a macrocyclic compound structure including a lactone or lactam moiety. While it preferably has at least some T-cell immunomodulating or immunosuppressant activity, it may also exhibit concomitantly or predominantly further pharmaceutical properties, such as anti-inflammatory activity.

A calciferol is to be understood herein as being a vitamin D or a compound structurally related to a vitamin D, either natural or synthetic.

The compositions of the invention may be adapted for systemic, e.g. oral or intravenous, or for topical use; preferably they are adapted for topical use. They are useful for the known indications of the particular active agents incorporated therein. They are particularly indicated for use in dermatological diseases, e.g. dermatological diseases which have an inflammatory component or involve inflammatory complications, such as atopic dermatitis, psoriasis and acne, or in inflammatory bowel disease (IBD).

A suitable **macrolide T-cell immunomodulator or immunosuppressant** is for example an FKBP12-binding calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor, in particular an **asco-** or **rapamycin**. It preferably is an ascomycin. While the macrolide preferably has at least some calcineurin- or mitogen-activated kinase modulating or inhibiting activity, it may also exhibit concomitantly or predominantly further pharmaceutical properties, such as antiinflammatory activity. It preferably is a compound, e.g. an ascomycin, having rather long-acting activity relatively to other members of the same structural class, e.g. it is metabolically degraded slowly to inactive products.

An asco- or rapamycin is to be understood as asco- or rapamycin as such, or a derivative thereof. An asco- or rapamycin derivative is to be understood as being an antagonist, agonist or analogue of the parent compound which retains the basic structure and modulates at least one of the biological, for example immunological properties of the parent compound.

An "anti-inflammatory ascomycin derivative" is defined herein as an ascomycin derivative that exhibits pronounced anti-inflammatory activity in e.g. animal models of allergic contact dermatitis but has only low potency in suppressing systemic immune response, namely, which has a minimum effective dose (MED) of up to a concentration of about 0.04 % w/v in the murine model of allergic contact dermatitis upon topical administration, while its potency is at least 10 times lower than for tacrolimus (MED 14 mg/kg) in the rat model of allogeneic kidney transplantation upon oral administration (Meingassner, J.G. et al., Br. J. Dermatol. 137 [1997] 568-579; Stuetz, A. Seminars in Cutaneous Medicine and Surgery 20 [2001] 233-241). Such compounds are preferably lipophilic.

Suitable **ascomycins** are e.g. as described in EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 523088, EP 532089, EP 569337, EP 626385, WO 93/5059 and WO 97/8182;
in particular:

- **ascomycin**;
- **tacrolimus** (FK506; Prograf^{R});
- **imidazolylmethoxyascomycin** (WO 97/8182 in Example 1 and as compound of formula I);
- **32-O-(1-hydroxyethylindol-5-yl)ascomycin** (L-732531) (Transplantation 65 [1998] 10-18, 18-26, on page 11, Figure 1; and

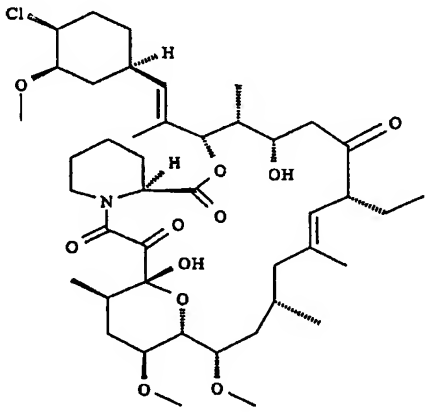
- **(32-desoxy,32-epi-N1-tetrazolyl)ascomycin** (ABT-281) (J.Invest.Dermatol. 12 [1999] 729-738, on page 730, Figure 1);

preferably:

- {1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R}-17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0(4,9)]octacos-5,18-diene-2,3,10,16-tetraone (Example 8 in EP 626385), hereinafter referred to as **"5,6-dehydroascomycin"**;
- {1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16,20-trihydroxy-4-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-azatricyclo[18.6.1.0(1,22)]heptacos-10-ene-2,8,21,27-tetraone (Examples 6d and 71 in EP 569337), hereinafter referred to as **"ASD 732"**;

and especially

- **pimecrolimus** (INN recommended) (ASM981; Elidel™), i.e. {[1E-(1R,3R,4S)]1R,9S,12S, 13R,14S,17R,18E, 21S,23S,24R,25S,27R}-12-[2-(4-chloro-3-methoxycyclohexyl)-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28,dioxa-4-azatricyclo [22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetraone, of formula I



(Example 66a in EP 427680),

hereinafter also referred to as **"33-epichloro-33-desoxyascomycin"**.

Suitable anti-inflammatory ascomycin derivatives are e.g.: (32-desoxy-32-epi-N1-tetrazolyl)ascomycin (ABT-281); 5,6-dehydroascomycin; ASD 732; and pimecrolimus.

Suitable **rapamycins** are e.g. as described in USP 3'929'992, WO 94/9010 and USP 5'258'389, preferably **sirolimus** (rapamycin; Rapamune^R) and **everolimus** (RAD001; Certican^R).

A particularly preferred macrolide T-cell immunomodulator or immunosuppressant is **pimecrolimus**; it is in free form unless specified otherwise.

A suitable **calciferol** is for example:

- calciferol, the synthetic form of vitamin D, as such (vitamin D2; ergocalciferol; Deltalin^R);
- calcipotriol (Daivonex^R; calcipotriene);
- calcitriol (1α,25-dihydroxycholecalciferol; 1α,25-dihydroxyvitamin D3; Rocaltrol^R);
- cholecalciferol (vitamin D3; Trivitan^R);
- 22,23-dihydroergocalciferol (vitamin D4; 22,23-dihydrovitamin D2);
- 25-hydroxycholecalciferol;
- 25-hydroxyergocalciferol;
- maxacalcitol;
- falecalcitol or falecalcitriol (ST-630; F6VD3; flocalcitriol; Penedrem^R); or
- tacalcitol (1α,24R-dihydroxycholecalciferol; 1α,24R-dihydroxyvitamin D3; Bonalfa^R);

preferably calcipotriol or tacalcitol, especially calcipotriol.

Subgroups of compositions of the invention comprise a macrolide T-cell immunomodulator or immunosuppressant, preferably an anti-inflammatory ascomycin derivative as defined above, especially pimecrolimus, in combination or association with a calciferol other than the following calciferols singly or collectively in any number:

- calcitriol; and/or
- calcipotriol; and/or
- tacalcitol.

In a further subgroup of compositions of the invention the macrolide T-cell immunomodulator or immunosuppressant is other than tacrolimus; in a further subgroup it is other than tacrolimus and sirolimus.

Preferred for use in the treatment of conditions where inflammation is involved are compositions of the invention wherein one or both components possess some degree of inherent anti-inflammatory activity. Particularly preferred are compositions comprising an ascomycin in combination or association with a calciferol, especially 33-epichloro-33-desoxyascomycin in combination or association with calcipotriol or tacalcitol. The inflammatory condition is e.g. atopic dermatitis, psoriasis or acne, or IBD.

"Treatment" as used herein includes prevention, namely prophylactic as well as curative treatment.

For the treatment of dermatological conditions the calciferol preferably is administered topically.

Synergy is e.g. calculated as described in Berenbaum, Clin. Exp. Immunol. 28 (1977) 1, using an interaction term to correct for differences in mechanism between the two drugs, as described in Chou et al., Transpl. Proc. 26 (1994) 3043. The index of synergy is calculated as:

$$\frac{\text{dose of A}}{A_E} + \frac{\text{dose of B}}{B_E} + \frac{\text{(dose of A) x (dose of B)}}{A_E \times B_E}$$

in which the doses of the compounds A and B represent those used in a particular combination, and A_E and B_E are the individual doses of A and B respectively giving the same effect. If the result is less than 1, there is synergy; if the result is 1, the effect is additive; if the result is greater than 1, A and B are antagonistic. By plotting an isobologram of dose of A / A_E vs. dose of B / B_E the combination of maximum synergy can be determined. The synergistic ratio expressed in terms of the ratio by weight of the two compositions at synergistic amounts along the isobologram, especially at or near the point of maximum synergy, can then be used to determine formulations containing an optimally synergistic ratio of the two compounds.

Assays which may be employed are e.g. conventional assays known for determination of the pharmacological activity of the components of the compositions individually, e.g. as described in EP 0 427680, Br. J. Dermatol. 137 (1997) 568-573 or Br. J. Dermatol. 141 (1999) 264-273, or for inhibition of keratinocyte proliferation and vitamin D metabolism, e.g. as described in EP 0 683156.

The invention also provides products and methods for co-administration of a macrolide T-cell immunomodulator or immunosuppressant, e.g. 33-epichloro-33-desoxy-ascomycin or 5,6-dehydroascomycin, and a calciferol, e.g. calcipotriol or tacalcitol or, at synergistically effective dosages, e.g.:

- a method of treatment or prevention of a dermatological disease such as atopic dermatitis, acne and psoriasis, or of IBD, in a subject suffering from or at risk for such condition, comprising co-administering synergistically effective amounts of a composition of the invention;
- the use of a macrolide T-cell immunomodulator or immunosuppressant in the manufacture of a medicament for co-administration in synergistically effective amounts with a calciferol;
- the use of a calciferol in the manufacture of a medicament for co-administration in synergistically effective amounts with a macrolide T-cell immunomodulator or immunosuppressant;
- a kit of parts comprising a macrolide T-cell immunomodulator or immunosuppressant and a calciferol in separate unit dosage forms, preferably wherein the unit dosage forms are suitable for administration of the component compounds in synergistically effective amounts, together with instruction for use, optionally with further means for facilitating compliance with the administration of the component compounds, e.g. a label or drawings;
- the use of a macrolide T-cell immunomodulator or immunosuppressant in the manufacture of a pharmaceutical kit which is to be used for facilitating co-administration with a calciferol;
- the use of a calciferol in the manufacture of a pharmaceutical kit which is to be used for facilitating co-administration with a macrolide T-cell immunomodulator or immunosuppressant;
- a macrolide T-cell immunomodulator or immunosuppressant and a calciferol as a combined pharmaceutical preparation for simultaneous, separate or sequential use, preferably in synergistically effective amounts, e.g. for the treatment or prevention of a dermatological disease such as atopic dermatitis, acne and psoriasis, or of IBD;
- a pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant in combination or association with a calciferol, e.g. in synergistically effective amounts, together with at least one pharmaceutically acceptable diluent or carrier,

e.g. for use in treatment or prevention of a dermatological disease such as atopic dermatitis, acne and psoriasis, or of IBD; and

- a process for the preparation of a composition of the invention comprising mixing a macrolide T-cell immunomodulator or immunosuppressant and a calciferol, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

By "synergistically effective amounts" is meant an amount of macrolide T-cell immunomodulator or immunosuppressant and an amount of a calciferol which are individually below their respective effective dosages for a relevant indication, but which are pharmaceutically active on co-administration, e.g. in a synergistic ratio, for example as calculated above. Furthermore, "synergistically effective amounts" may mean an amount of macrolide T-cell immunomodulator or immunosuppressant and an amount of a calciferol which are individually equal to their respective effective dosages for a relevant indication, and which result in a more than additive effect.

The molar amount of macrolide T-cell immunomodulator or immunosuppressant present is from roughly similar to, to significantly more than the amount of a calciferol, preferably twice as much or more. Synergistic ratios of macrolide T-cell immunomodulator or immunosuppressant to calciferol by weight are thus suitably from about 1000:1 to about 1:10, preferably from about 500:1 to about 1:1, most preferably from about 200:1 to about 20:1, e.g. about 100:1.

The compositions of the invention can be administered as a free combination, or the drugs can be formulated into a fixed combination, which greatly enhances the convenience for the patient.

Absolute dosages of the compounds will vary depending on a number of factors, e.g. the individual, the route of administration, the desired duration, the rate of release of the active agent and the nature and severity of the condition to be treated. For example, the amount of active agents required and the release rate thereof may be determined on the basis of known in vitro and in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

For example, in prevention and treatment of a dermatological disease such as atopic dermatitis, acne and psoriasis, or of IBD, an initial dosage of about 2-3 times the maintenance dosage is suitably administered, followed by a daily dosage of about 2-3 times the maintenance dosage for a period of from one to two weeks, and subsequently the dose is gradually tapered down at a rate of about 5 % per week to reach the maintenance dosage. In general, synergistically effective amounts of 33-epichloro-33-desoxyascomycin and calcipotriol on oral administration for use in prevention and treatment of atopic dermatitis, acne or psoriasis, or of IBD, in larger animals, e.g. man, are amounts of 33-epichloro-33-desoxyascomycin of up to about 2 mg/kg/day, e.g. from about 0.01 mg/kg/day to about 2 mg/kg/day, preferably about 0.5 mg/kg/day, in combination or co-administration with amounts of calcipotriol of up to about 50 mg/kg/day, e.g. from about 0.25 mg/kg/day to about 50 mg/kg/day, preferably about 2.5 mg/kg/day, in a synergistic ratio, as described. Suitable unit dosage forms for oral co-administration of these compounds thus may contain on the order of from about 0.5 mg to about 100 mg, preferably about 3 mg to about 30 mg of 33-epichloro-33-desoxyascomycin, and from about 10 mg to about 3000 mg, preferably about 50 mg to about 500 mg of calcipotriol. The daily dosage for oral administration is preferably taken in a single dose, but may be spread out over two, three or four dosages per day. For i.v. administration, the effective dosage is lower than that required for oral administration, e.g. about one fifth the oral dosage.

By "co-administration" is meant administration of the components of the compositions of the invention together or at substantially the same time, e.g. within fifteen minutes or less, either in the same vehicle or in separate vehicles, so that upon oral administration, for example, both compounds are present simultaneously in the gastrointestinal tract. Preferably, the compounds are administered as a fixed combination.

The compositions of the invention include compositions suitable for administration by any conventional route, in particular compositions suitable for administration either enterally, for example, orally, e.g. in the form of solutions for drinking, tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions; or topically, e.g. for the treatment of inflammatory conditions of the skin or mucosae, e.g. in the form of a dermal cream, ointment, ear drops, mousse, shampoo, solution, lotion, gel, emulgel or like preparation, especially in combination or association with penetration enhancing agents, as

well as for application to the eye, e.g. in the form of an ocular cream, gel or eye-drop preparation, for treatment of inflammatory conditions of the lungs and airways, e.g. in the form of inhalable compositions, and for mucosal application, e.g. in the form of vaginal tablets.

A topical formulation may comprise from about 0.0001 % to about 5 % by weight of each pharmaceutically active component, preferably from about 0.1 % to about 5 % macrolide and from about 0.0001 % to about 1 % calciferol; preferably from about 0.5 % to about 2 % macrolide and from about 0.0003 % to about 0.01 % calciferol; e.g. from about 0.5 % to about 2 % pimecrolimus and from about 0.0001 % to about 0.005 % calcitriol or from about 0.001 % to about 0.05 % calcipotriol.

Compositions adapted for topical administration, preferably to skin, are preferred.

The compositions of the invention are suitably emulsions, microemulsions, emulsion preconcentrates or microemulsion preconcentrates, or solid dispersions, especially water-in-oil microemulsion preconcentrates or oil-in-water microemulsions, comprising the macrolide T-cell immunomodulator or immunosuppressant and the calciferol in a synergistic ratio.

The compositions of the invention can be prepared in conventional manner, e.g. by mixing a macrolide T-cell immunomodulator or immunosuppressant and a calciferol, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

The active agent components may be in free form or pharmaceutically acceptable salt form as appropriate.

While the invention primarily contemplates combination or association of just two pharmaceutically active components, it does not exclude the presence of further active agents, e.g. one further active agent, as far as they do not contradict the purpose of the present invention.

The following Example illustrates the invention. The compounds are in free, i.e. neutral or base form unless specified otherwise.

Example: **Cream**

A cream with dissolved 33-epichloro-33-desoxyascomycin is prepared in conventional manner with calcipotriol, both in a 1 % w/w concentration, and contains the following ingredients:

Component	Amount (g)
33-Epichloro-33-desoxyascomycin	1.00
calcipotriol	0.005
triglycerides, medium chain	15.00
oleyl alcohol	10.00
sodium cetylstearyl sulfate	1.00
cetyl alcohol	4.00
stearyl alcohol	4.00
glyceryl monostearate	2.00
benzyl alcohol	1.00
propylene glycol	5.00
citric acid	0.05
sodium hydroxide	*
water	ad 100.0

* amount required to adjust pH to 5.5

The preparation follows the conventional manufacturing procedures for an emulsion. The ascomycin is added to the heated homogeneous oily phase which contains triglycerides medium chain, oleyl alcohol, sodium cetylstearyl sulfate, cetyl alcohol , stearyl alcohol and glyceryl monostearate. In parallel, the water phase containing calcipotriol, benzyl alcohol, propylene glycol, citric acid and sodium hydroxide is heated at the same temperature as the oily phase. The oily phase is added to the water phase and homogeneisation is performed. The resultant cream is cooled to room temperature.

Claims:

1. A pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant in combination or association with a calciferol, together with at least one pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1 comprising 33-epichloro-33-desoxyascomycin in combination or association with calcipotriol or tacalcitol.

3. A method of treatment of a dermatological disease such as atopic dermatitis, acne or psoriasis, or of inflammatory bowel disease (IBD), in a subject suffering from or at risk for such condition, comprising co-administering a synergistically effective amount of a composition according to claim 1.

4. A process for the preparation of a composition according to claim 1 comprising mixing a macrolide T-cell immunomodulator or immunosuppressant and a calciferol, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

5. A kit of parts comprising a macrolide T-cell immunomodulator or immunosuppressant and a calciferol in separate unit dosage forms, together with instructions for use.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003512

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/593 A61K31/453 A61P17/00 A61P1/00
//(A61K31/593,31:453)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used).
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/18468 A (AMERICAN HOME PROD) 7 May 1998 (1998-05-07) page 8, lines 25-36; claims 1,4-6,8	1-5
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 June 2004	29. 07. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tardi, C

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 99/24036 A (ORMEROD ANTHONY DAVID ; UNIV ABERDEEN (GB); WINFIELD ARTHUR (GB)) 20 May 1999 (1999-05-20) claims 1,4,7	1-5
A	WO 02/089796 A (MOORE HENRIETTA DENISE ; CORDIER ANDRE (CH); NOVARTIS AG (CH); KEHREN) 14 November 2002 (2002-11-14) claims 3,12	1-5
A	PATENT ABSTRACTS OF JAPAN vol. 1996, no. 03, 29 March 1996 (1996-03-29) & JP 7 291868 A (TEIJIN LTD), 7 November 1995 (1995-11-07) abstract	1-5
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A	LEWIS H M: "THERAPEUTIC PROGRESS II: TREATMENT OF PSORIASIS" JOURNAL OF CLINICAL PHARMACY AND THERAPEUTICS, BLACKWELL SCIENTIFIC PUBLICATION, OXFORD, GB, vol. 19, no. 4, 1 August 1994 (1994-08-01), pages 223-232, XP000576425 ISSN: 0269-4727 page 225, column 2 - page 226, column 1	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/003512

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/003512

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/003512

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